REMARKS

The Claim Amendments

Applicants have amended claim 1 to recite an isolated polynucleotide encoding a variant cytochrome P450 3A4 (CYP3A4) monooxygenase polypeptide or fragment thereof, wherein the variant polypeptide encoded by the polynucleotide has an impaired expression and impaired enzymatic activity compared to the corresponding wild type CYP3A4 polypeptide. These amendments are supported throughout the specification. The impaired expression is supported, e.g., at pages 38-39, Example 6, which teaches the functional consequences of specific protein variants of CYP3A4, wherein the variant CYP3A4 polypeptide containing the T to M change at residue 363 ("T363M") has a diminished expression, at levels less than 10% of the wild-type CYP3A4, as assessed by measuring reduced CO difference spectra. The variant also exhibited a reduced expression as assessed by Western Blotting using an anti CYP3A12 polyclonal antibody known to cross-react with CYP3A4. See, Figure 7, showing an immunoblot of wild-type CYP3A4 and the M5 variant, where the variant is represented by a faint 54 kDA band compared to the wild-type. The impaired enzymatic activity is supported, e.g., page 39, lines 3-4 and Tables 5-7, which teaches that the catalytic activity of the M5 variant was strongly impaired (at activity levels that were approximately half that of the wild-type protein) by measurement with testosterone, progesterone and 7-benzyloxy-4-(trifluoromethyl)coumarin (7-BFC).

Applicants have amended claim 3 to delete reference to an amino acid deletion or addition, as requested by the Examiner.

Applicants have amended claim 7 to replace protein with polypeptide to improve its form and maintain consistency.

Applicants have amended claim 12 to improve its form and make reference to a nucleic acid fully complementary to a polynucleotide, as requested by the Examiner.

Applicants have amended claim 37 to recite a primer or probe consisting of an oligonucleotide of about 15 to 50 nucleotides in length and comprising a fragment of the polynucleotide of claim 1 or a fully complementary sequence thereof wherein said fragment comprises SEQ ID NO:90. This amendment improves the form of the claim.

Applicants make these amendments expressly without waiver of their right to file for and to obtain claims directed to the cancelled or amended subject matter in this application or in divisional or continuing applications claiming priority and benefit herefrom.

None of the amendments to the claims constitutes new matter. Their entry is requested. Upon entry of these amendments, claims 1, 4-8, 34, 36 and 37 are now pending in this application.

The Office Action

Claim Rejections

35 U.S.C. §112, Second Paragraph – Indefiniteness

Claims 1, 3-8, 12-13, 37 and 39-40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite for reciting the term "CYP3A4". The Examiner acknowledges that "applicants have discovered a phenotypic change in a variant of the cytochrome P450 3A4 monooxygenase gene" and that "the specification refers to the sequence

of CYP3A4 by GenBank accession number CYP3A4." However, the Examiner asserts that the different laboratories may use the same laboratory designation to define distinct molecules and that the use of the laboratory designation CYP3A4 renders the claim indefinite. The Examiner has stated that a deposit of the gene listed in claim 1 would satisfy the enablement requirements. Applicants traverse in view of the claim amendments and following remarks.

Pursuant to a telephone interview between the undersigned and Examiners Fetterolf and Siew on June 20, 2006, applicants believe that by providing the complete name of the variant cytochrome P450 3A4 (CYP3A4) monooxygenase gene, along with its GenBank accession number, it would be clear to one of skill in the art - on this basis alone - what gene is being referred to.

Moreover, applicants have amended independent claim 1, and the claims that depend therefrom, to recite that the polypeptide or fragment thereof has an impaired expression and impaired enzymatic activity compared to the corresponding wild type CYP3A4 polypeptide. This claim amendment is fully supported by the specification, as indicated above. Accordingly, applicants request that the Examiner reconsider and withdraw this objection.

Claim 3 also stands rejected under 35 U.S.C. §112, second paragraph, as allegedly having insufficient antecedent basis for the recitation of an addition and/or deletion of a nucleotide in the claim. Applicants have obviated the objection by amending claim 3 to delete reference to an addition and/or a deletion of a nucleotide sequence.

35 U.S.C. § 102(e) - Anticipation

Larossa and Mittman

Claims 1, 4-7, 12-13, 37 and 39-40 stand rejected under 35 U.S.C. §102(e) as being anticipated by Larossa et al., U.S. Patent 6,025,131 ("Larossa"). Claim 37 stands rejected under 35 U.S.C. §102(e) as being anticipated by Mittman et al., U.S. Patent 6,821,724 ("Mittman"). While the Examiner acknowledges that Larossa does not refer to a polynucleotide which encodes a variant of a CYP3A4 polypeptide or fragment thereof, the Examiner maintains that Larossa still teaches a polynucleotide encompassing the nucleotide sequence of SEQ ID NO:90, as well as a vector comprising the polynucleotide, host cells with a vector, a nucleic acid molecule complementary to the polynucleotide, a diagnostic composition comprising the polynucleotide, and a method for producing cells comprising the polynucleotide. The Examiner also states that Mittman refers to a nucleic acid probe that comprises the nucleotide sequence of SEQ ID NO:90, or a complementary sequence thereof. Applicants traverse, in view of the claim amendments and the below remarks.

Claim 1, prior to the amendment made herein, was directed to an isolated polynucleotide encoding a variant cytochrome P450 3A4 (CYP3A4) monooxygenase polypeptide or fragment thereof wherein the polynucleotide was selected from a group of polynucleotides, one of which was a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 90. As stated earlier, applicants have discovered a phenotypic change associated with an amino acid substitution resulting from a nucleotide change in a variant of the CYP3A4 gene. A portion of the CYP3A4 nucleotide sequence containing the polymorphism that produces the variant polypeptide with an impaired expression and enzymatic activity is provided in SEQ ID NO:90. Neither Larossa nor Mittman describe or refer to a CYP3A4 polypeptide. Neither of the sequences referred to in Larossa and Mittman is within a CYP3A4-encoding sequence. These

documents, therefore, cannot anticipate the subject matter of a claim directed to an isolated polynucleotide that comprises the nucleotide sequence of SEQ ID NO:90 and encodes a variant CYP3A4 polypeptide or fragment.

However, in the interest of advancing prosecution, applicants have even further obviated the above rejections. As amended, claim 1 recites that the polypeptide encoded by the polynucleotide has impaired expression and enzymatic activity compared to the corresponding wild type CYP3A4 polypeptide. Applicants have also amended claim 37 to recite that the primer or probe consists of an oligonucleotide of about 15 to 50 nucleotides in length and comprises a fragment of the polynucleotide of claim 1 or a fully complementary sequence thereof wherein said fragment comprises the nucleotide sequence of SEQ ID NO:90. Applicants therefore request that the Examiner withdraw these rejections.

Conclusion

Applicants request favorable consideration and early allowance of the elected claims.

Respectfully submitted,

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